Contents lists available at Science Direct

International Journal of Biological Macromolecules

journal home page: http://www.elsevier.com/locate/ijbiomac

New insight into the allosteric effect of L-tyrosine on mushroom tyrosinase during L-dopa production

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Kinetics studies of L-tyrosine (LTy) ortho-hydroxylation by mushroom tyrosinase (MT) confirmed that MT wasseverely, but not completely, inhibited at higher concentrations of LTy. Despite the availability of the crystalstructure reports, no allosteric site has been identified on MT. To examine the assumption that a non-specificbinding site works as a regulatory site, docking simulations were run for the second molecule of L-tyrosine(LTy2) on the complexes of thefirst L-tyrosine molecule (LTy1) with the heavy chain (H) of MT (LTy1/HMT)and its dimerwith the light chain (Ty1/LHMT). Inboth, LTy2occupied a non-specific binding site (MTPc). MD sim-ulations revealed LTy2/HMT/LTy1and LTy2/LHMT/LTy1were stable. Binding free-energy analysis supported theformation of LTy2/HMT/LTy1and LTy2/LHMT/LTy1at higher concentrations of LTy and disclosed the importanceofΔEelecandΔGpolarduring binding of LTy2to MTPc. Upon LTy2binding to MTPc, the Cu-Cu distance remainedunchanged while the spatial position of LTy1in the active site (MTPa) changed so that it would not be able to par-ticipate inortho-hydroxylation.Thisstudy suggests a tuning rolefor L chainduringbindingof the ligandstoMTPaand MTPc. Given these results, a plausible mechanism was proposed for the MT substrate inhibition.

Keywords: Substrate inhibition Regulatory site Non-specific binding site